RESPONSE TO FINAL OFFICE ACTION

A. Status of the Claims

Claims 1-7, 9, and 11-29 were pending at the time of the Office Action. Claims 8, 10, and 30-32 had been withdrawn from consideration as being drawn to a non-elected invention. Claims 1, 4, 28, and 29 are amended in the Amendment set forth herein. Support for the amendments can be found in the claims as originally filed. No new claims have been added, and no claims have been canceled. Thus, claims 1-7, 9, and 11-29 are presently under consideration.

B. Specification Objections

The specification has been objected to as being indefinite because the Examiner is unable to locate "equation 2" in the specification. In the Amendment set forth herein, Applicants have amended the paragraph beginning on page 12, line 1, to indicate that equation 2 refers to "eq 2" in the equation below this paragraph. Therefore, the objection to the specification is now moot and withdrawal of the objection is thus respectfully requested.

C. Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

The Action rejects claims 1-7, 9 and 11-29 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out the subject matter which Applicant regards as the invention. The individual rejections and Applicants' responses are set forth below.

(1) In claim 1, set (a), the Action indicates that the recitation of "isoprenyl azide substrate of at least first protein" is grammatically awkward and indefinite because it is not clear whether said "substrate" describes a substrate for said "azide" entity or whether the "substrate" describes a substrate for the "protein entity." Although Applicants disagree with the assertion, to expedite prosecution, Applicants have amended claim 1 to recite "obtaining a substrate of at least a first protein in said cell, wherein the substrate is a synthetic isoprenyl azide substrate

comprising at least a first azide," thus making it clear that the substrate is a substrate of the protein entity.

(2) In claim 1, step (b), the recitation of "incorporates into the first protein at least the first azide" is said to be indefinite as unclear whether/how a protein "incorporates" an azide moiety. In particular, it is said to not be clear whether an azide moiety is synthesized de novo on "the first protein" or whether the first protein is reacted with the first azide moiety. Although Applicants disagree the Examiner's assertion, Applicants, in an effort to expedite prosecution, have amended claim 1 to recite "contacting the cell with the synthetic isoprenyl azide substrate under conditions wherein the cell takes up the synthetic isoprenyl azide substrate and the synthetic isoprenyl azide substrate reacts with the first protein to produce at least a first isoprenylated protein." This rejection is now moot as it is clear that the first protein is reacted with the azide moiety.

(3) In claim 1, step (c), the Action asserts that "proteins produced by said cell with a phosphine capture reagent" is indefinite because it is not clear how cells produce proteins "with a phosphine capture reagent." In particular, it is said to not be clear whether the cell is contacted with a "phosphine capture reagent," or whether the cell produces "a phosphine capture reagent" endogenously. Although Applicants disagree with the Examiner's assertion, Applications, in an effort to expedite prosecution, have amended claim 1 to recite "detecting at least said first isoprenylated protein from proteins produced by said cell by contacting the proteins produced by said cell with a phosphine capture reagent, wherein capture occurs by the Staudinger reaction." This amendment makes it clear that the phosphine capturing reagent is not necessarily an endogenous component of the cell.

The Action also asserts that recitation of "proteins produced by said cells ... by the Staudinger reaction" is indefinite as not clear how cells produce proteins by "the Staudinger reaction." The amendment set forth above makes it clear that the cell is not producing proteins by the Staudinger reaction, but that the Staudinger reaction pertains to the mechanism of capture.

The Action further asserts that recitation of "detecting at least said first protein ... with a phosphine capture reagent" is indefinite as not clear whether the first protein is contacted with a phosphine moiety, or whether the first protein is produced with a phosphine moiety by the cell. The amendment set forth in part (c) of claim 1, discussed above, makes it clear that first protein is captured with a phosphine moiety.

(4) In claims 4-6, the recitation of "FPP" is said to lack antecedent basis. There is no need for antecedent basis of "FPP," because the limitation "wherein farnesyl diphosphate (FPP) is inhibited in said cell" is a new limitation that further defines the cell set forth in claim 1.

(5) Claims 5-6 are said to be indefinite as not be clear how "HMG Co-A reductase inhibitor" and "lovastatin" inhibit FPP. In response, the Examiner is directed to page 7, lines 12-26 of the disclosure, where the disclosure explains that metabolic incorporation of azido-farnesyl groups into farnesylated proteins could be increased by inhibition of endogenous synthesis of FPP by blocking HMG Co-A reductase using lovastatin. Thus, the limitations "HMG Co-A reductase inhibitor" and "lovastatin" are sufficient clear to meet the requirement of 35 U.S.C. §112, second paragraph.

(6) In claim 28, step (b), the recitation "the synthetic substrate is ... incorporated into the protein" is said to be indefinite because the recited molecular structures are said to not appear to be "incorporated into the protein" as required in line 2 of step b). Applicants note that claim 28 was amended to make it clear as to the structure of the synthetic substrate, and to clearly set

forth that the protein is labeled with the synthetic substrate via the azide moiety. Further, the language of the claim makes it clear that labeling is by virtue of the interaction between the synthetic substrate and the protein.

(7) In claim 29, the recitation of "the synthetic substrate ... is prenylated" is said to be indefinite as not clear how, or by what mechanism, the synthetic substrates having the molecular formulas recited in step b) are "prenylated." Claim 29 has been amended to omit reference to the synthetic substrate being prenylated.

In view of the foregoing, removal of the above rejections is respectfully requested.

D. Rejections Under 35 U.S.C. §103(a)

1. Rejection of claims 1-7, 9, 11, 13 and 15-24

The Action rejects claims 1-7, 9, 11, 13 and 15-24 under 35 U.S.C. §103 as being obvious over Spielmann *et al.* (US 6,284,910) in view of Saxon and Bertozzi (US 6,570,040). In particular, it is asserted that Spielmann *et al.* teach detecting an isoprenylated protein (citing col. 27, lines 14-1 5, "H-Ras farnesyl-group") in a cell (citing col. 27, line 12, "oocytes') by: obtaining a synthetic isoprenyl (citing col. 27, line 17, "farnesyl analogs") azide (citing col. 6, line 52, "N;) substrate of a protein (citing col. 26, line 3, "FTase"), contacting the cell under conditions wherein the cell takes up (see col. 27, line 18, "microinjection") and incorporates (citing col. 27, lines 16-17, "enzymatic methods to attach") into the protein (citing col. 27, line 17, "H-Ras") a first azide (citing col. 6, line 52, "N3") from the substrate (citing col. 27, line 17, "farnesyl analogs"), and detecting (citing col. 25, line 66, "Assay for Analog Transfer") said protein (citing col. 26, line 3, "FTase"). It is stated that Spielmann *et al.* do not teach "a phosphine capture reagent" or "the Staudinger reaction" but that Saxon & Bertozzi teach this element for detecting intracellular azido-target substrates (citing col. 14, line 57, "detectable labels", line 55, "intracellular", lines 52-53, "azido-target substrate"). Therefore, it is concluded

that it would be obvious to detect an isoprenylated protein according to Spielmann *et al.* with a phosphine capture reagent and the Staudinger reaction because Saxon & Bertozzi discovered that the Staudinger reaction is both selective and compatible with aqueous environments, thereby allowing *in vivo* applications (citing Abstract).

Applicants respectfully traverse. The claims are not obvious as one of skill in the art would have lacked a motivation to combine the cited references to arrive at the claimed invention absent impermissible hindsight reconstruction based on the teaching in the specification. Specifically, the Spielmann *et al.* reference deals with a different problem than that solved by the claimed invention. Spielmann concerns a specific FPP analog and therapeutic implications of this rather than detecting an isoprenylated protein in a cell as claimed. The analogs modify functional groups and thus the biological activity of prenyl-protein specific enzymes. *See, e.g.*, col. 28, l. 7-11. The Spielmann reference further deals in this regard narrowly with the "design and synthesis of a farnesylpyrophosphate (FPP) analog, 8-anilinogeranyl pyrophosphate (AGPP) that is transferred to Ras by farnesyltransferase (FTase), in which the omega-terminal isoprene unit of the farnesyl group has been replaced with an aniline functionality." It is further stated that:

> The compounds of this invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. These compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer.

Col. 11, l. 28-32. The application goes on to describe in great detail the formulation of pharmaceutical compositions for delivering such therapeutic agents. The patent thus relates to ***therapeutic rather than diagnostic applications*** and one of skill in the art would be ***without any motivation*** to combine this reference with Saxon & Bertozzi absent hindsight reconstruction.

The Examiner's citation of col. 12, Scheme 1 of Spielmann *et al.* does not pertain to any diagnostic application, but to therapeutic applications. Col. 12, lines 12-14 indicate that "[i]n one exemplary application, a suitable amount of compound is administered to a human patient undergoing treatment for cancer. This section of Spielmann *et al.* pertains to therapeutic applications, and thus would provide no motivation to one of ordinary skill in the art to combine this reference with Saxon & Bertozzi to provide for the claimed invention.

The citation of several sections of Spielmann pertaining to ethanol HCl precipitation and scintillation counting (col. 25, lines 18-19), incorporated radioactivity involving SDS gels, and reverse phase chromatography (col. 25, line 66) do not pertain to detection of isoprenylated proteins, but rather pertain to techniques used to investigate the mechanism of FTase inhibition by AGPP (see column 23, lines 60-61). Each of these techniques was performed in the conjunction of *in vitro* assays to study the reaction kinetics of FTase inhibition by AGPP.

While the paragraph bridging cols. 25 to 26 of Spielmann is cited that mentions a "continuous fluorescence assay," a further review demonstrates that this *in vitro* assay is of the ability to transfer FPP analogs to substrates by FTase, rather than detection of isoprenylated proteins, let alone detection of proteins from a cell. For example, the section states that "An important requirement for these studies is the development of a rapid technique for evaluating whether FPP analogs that are efficiently and appropriately transferred to target substrates by FTase. The analogs were evaluated for their ability to be transferred by FTase to the pentapeptide N-dansyl-GCVLS in a continuous fluorescence assay." The section therefore goes to confirming the ability to produce analogs, not detection of proteins. This therefore has no relevance to the claimed invention.

The Action also cites col. 27 as teaching *in vivo* application of the technique, yet this section deals with a different technique. The section indicates that what is microinjected is modified H-Ras, rather than a substrate of H-Ras. Although farnesylation of H-Ras is said to occur in vivo, this technique differs from that set forth in the claimed invention because it does not address the method that does not pertain to injection of a substrate of H-Ras. For example, it is stated that "The approach makes use of enzymatic methods to attach structurally related farnesyl analogs onto the prenylation site of H-Ras combined with microinjection procedures to study their *in vivo* function." Col. 27, l. 15-19. The technique is used to examine the biological activity of the analog, not detect an isoprenylated protein in a cell, this section stating that "the system provides a method to study the *in vivo* role of prenylation by analyzing the ability of FPP analogues to rescue H-Ras biological functions in isoprenoid-depleted oocytes."

Furthermore, regarding the *in vivo* application, it is possible that AGPP's *in vivo* function could be caused by activation or inhibition of other cellular proteins rather than due to its function as a substrate for protein farnesylation. This possibility, which would be known to one of ordinary skill in the art, is not addressed in Spielmann. Further, it is noteworthy that the chemical nature of lipid-modified Ras using the compounds described in Spielman has never been conclusively established *in vivo*.

Further, regarding Saxon and Bertozzi, it is not clear that its teachings pertaining to use of a phosphine capture reagent and the Staudinger reaction can be applied in a hydrophobic environment. There is not established that Saxon and Bertozzi provides any motivation to one of ordinary skill in the art to apply its teachings pertaining to glycoproteins (i.e., a hydrophilic environment) to farnesylated proteins (i.e., a hydrophobic environment). One of ordinary skill in

the art would know that the farnesyl group is very hydrophobic, and the azide moiety could be buried inside a protein to form a micelle structure.

In sum, one of skill in the art would have been without any motivation to combine the cited references based on the prior art and absent application of impermissible hindsight reconstruction. *See In re Carroll*, 202 USPQ 571 (CCPA 1979) ("One of the more difficult aspects of resolving questions of non-obviousness is the necessity 'to guard against slipping into the use of hindsight.'"), citing *Graham v. John Deere Co.*, 148 USPQ 459 (U.S. Sup. Ct. 1965). In order to establish a *prima facie* case of obviousness under 35 U.S.C. §103 "substantial evidence" demonstrating the motivation to combine the references must be shown on the record. *See In re Vaeck*, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991), *see also In re Zurko*, 59 USPQ 2d 1693 (Fed. Cir. 2001). As such evidence is lacking, removal of the rejection is respectfully requested.

As to the Action's separate comments with respect to claims 3-7, 9, 11, 13, and 15-23, Applicants note that each of these claims depends from claim 1 and incorporates all limitations of this claim. As the Action's separate comments with respect to Spielmann *et al.* and Saxon & Bertozzi, the citations in these references do nothing to cure the shortcomings with respect to claim 1. Thus, these claims are nonobvious for the reasons set forth above. Removal of the rejection is thus respectfully requested.

2. Rejection of claim 12

Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Spielmann *et al.* (US 6,284,910) and Saxon & Bertoui (US 6,570,040) as applied to claim 1, and further in view of Lodish *et al.*, MOLECULAR CELL BIOLOGY, 4th ed., W.H. Freeman & Co. (1999). In particular, it is stated that Spielmann *et al.* and Saxon & Bertoui teach detecting an isoprenylated protein as described supra but do not teach Western blot detection. It is stated that Lodish *et al.*

teach this element for detecting a particular protein in a mixture (see Section 3.5) and thus it would be obvious to detect an isoprenylated protein with Western blot detection because Lodish *et al.* teach Western analysis is "one of the most powerful methods for detecting a particular protein" combining "superior resolving power of gel electrophoresis, the specificity of antibodies, and the sensitivity of enzyme assays."

In response, Applicants note that claim 12 depends from claim 1 and incorporates all limitations of the claim. As the rejection does nothing to cure the shortcomings with respect to claim 1, claim 12 is by definition also nonobvious for the reasons set forth above. Removal of the rejection is thus respectfully requested.

3. Rejection of claim 14

The Action rejects claim 14 under 35 U.S.C. 103(a) as obvious over Spielmann *et al.* (US 6,284,910) and Saxon & Bertozzi (US 6,570,040) as applied to claims 1 and 13, and further in view of Holmes, 62 J. ORG. CHEM. 2370 (1 997). Spielmann *et al.* and Saxon & Bertozzi are said to teach detecting an isoprenylated protein and Saxon & Bertozzi additionally a cleavable linker. It is stated that these do not teach a photocleavable linker but that Holmes teaches photocleavable linkers for anchoring biomolecules to solid supports. Therefore, it is concluded that it would be obvious to replace the cleavable linker of Saxon & Bertozzi with a photocleavable linker because Holmes states that photocleavable linkers are "particularly attractive in combinatorial library screening," as they result in biomolecules that are free of cleavage reagents.

In response, Applicants note that claim 14 depends from claim 1 and incorporates all limitations of the claim. As the rejection does nothing to cure the shortcomings with respect to claim 1, claim 14 is by definition also nonobvious for the reasons set forth above. Removal of the rejection is thus respectfully requested.

In view of the foregoing, Appellants respectfully request the removal of the rejection under 35 U.S.C. § 103.

E. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the undersigned (512)536-5639 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,

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